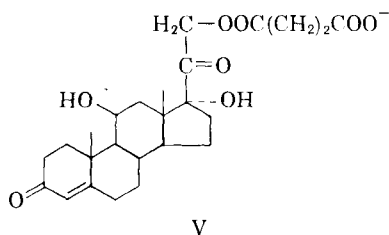


which would make a significant contribution to the total hydrolysis rate at lower pH values, specifically in the neutral pH region 4-7 as a function of pKa. This phenomenon had been indicated previously for hydrocortisone hemisuccinate(V) (4).



Thus the predicted stabilities (Table III) of the β, β' -dimethylglutarate hemiesters of these steroids at pH values closer to neutrality are the most optimistic estimates. Intramolecular catalysis, if present, would tend to increase the hydrolysis rate at neutral pH values over that predicted from specific hydroxyl ion catalysis alone.

As was expected, stability to specific hydroxyl ion catalyzed hydrolysis is greatly enhanced by alkyl

substitution over that for the hemisuccinate or other straight chain aliphatic hemiesters (4, 7) and is in accordance with Newman's rule (5, 6). It is interesting to note, however, that if intramolecular catalyzed hydrolysis is present, and significantly contributes in the neutral pH region 4-7, it would be predicted to be greater in the case of the alkyl substituted esters than for the nonalkylated hemiesters of dicarboxylic acids such as the straight chain glutaric or succinic acids (11).

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Solubilization in Nonpolar Solvents

Influence of the Chain Length of Solvent on the Solubilization of Water by Dioctyl Sodium Sulfosuccinate

By W. I. HIGUCHI and JAGDISH MISRA

The water solubilizing capacities of the solutions of dioctyl sodium sulfosuccinate (Aerosol OT, AOT) in normal aliphatic hydrocarbon solvents from *n*-heptane to *n*-octadecane were determined as functions of the AOT concentration and temperature. The method involved adding water to the AOT solutions up to the turbidity point. The solubilizing capacity was found to be strongly dependent on the solvent chain length, increasing with decreasing chain length. For example, in octane solutions at 30° about 50 moles of water per mole AOT can be solubilized while only 5 moles can be solubilized in hexadecane solutions. The thermodynamic activity of the solubilized water was determined by a modified isopiestic method. These data indicated that the binding of water in all systems studied was essentially the same. A tentative theory based on the solvation of the micelle exterior is proposed to explain the two sets of data.

THE PHENOMENON of micellar solubilization in aqueous systems has received considerable attention, this subject having recently been covered extensively in a book by McBain and Hutchinson (1). The applications of the principles and concepts of solubilization in aqueous media to pharmacy have been demonstrated (2).

The drug activity, release characteristics, and stability (3, 4) may be improved by a suitable choice and amount of these solubilizing agents.

There appears to have been little or no study of micellar solubilization of drugs in nonaqueous systems. It is not implied by this statement that the practice of pharmacy has not involved the use of this type of solubilization. However, the mechanisms of incorporation of water and highly polar drugs in hydrophobic vehicles by agents have not received much consideration. One should know whether the formulation is

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truly physically stable thermodynamically or whether the system is an emulsion or a suspension capable of physical degradation. The questions of how much bound water and drug are there and what are their states of binding should be of concern. The results of an investigation along these lines would be helpful in the understanding and in the improvement of oil base formulations, e.g., ointments, lotions, oil injections, etc.

It was decided that a water-surfactant-hydrocarbon compatibility study would be a most worthwhile starting point. Specifically, the aims were to show how much water might be incorporated into an oil with the help of a surfactant and how available such water might be for drug solubilization. Results of this investigation are reported in this communication.

EXPERIMENTAL

General Considerations.—The surfactant used in these studies was dioctyl sodium sulfosuccinate (di-2-ethylhexyl sodium sulfosuccinate).¹ It was selected because some of its micellar characteristics in nonaqueous solvents had been studied by others (5–7). The oils used for this work were some of the normal aliphatic hydrocarbons from heptane to octadecane. These were chosen because preliminary studies had indicated a rather unusual chain length-solubilization limit relationship, *viz.*, that in shorter chain solvents a great deal more water could be solubilized by the same amount of AOT.

Materials.—In preliminary studies "100% pure" AOT was used after removing the methanol-insoluble fraction. However, the end points (turbidity point) in the water solubilization experiments were not reproducible² with this purification procedure despite the fact that the carbon, hydrogen, and sulfur analyses indicated better than 99% purity in these samples. Therefore, the following procedure was followed which is a modification of that reported by Williams, Woodberry, and Dixon (8).

About 400 Gm. of AOT was dissolved in 800 ml. of methanol. The insoluble solids were centrifuged and the supernatant removed by decantation and cooled to 3°. To this solution was added about 1.4 L. of water cooled to 3°. The resulting precipitate was centrifuged out at 5° and discarded. Then 0.2 L. more of water at 3° was added to the solution and about 100 to 150 Gm. of the resulting precipitate was recovered by, again, centrifugation. The material was dried under vacuum at 75° to 85° for 2 to 3 days until further drying showed no loss in weight of the material. Samples prepared in this manner always gave the same mole-mole (water-to-surfactant) ratio to within about $\pm 2\%$.

All of the hydrocarbons used in this work were Eastman practical grade. These were dried and redistilled. Essential purity in all cases was established by melting point determinations. Doubly distilled water was used.

Procedure for Solubilization Limit Study.—To determine the amount of water that could be solubilized before the system became two-phase the following procedure was adopted. Water was added to about 30 ml. of a magnetically stirred AOT-hydrocarbon solution in water-jacketed 250-ml. flasks until turbidity and two-phase formation occurred. In all cases the end point was sharp (within 1% of added water) and reversible. At the end point the systems were initially turbid, but after a few minutes, two separate, relatively non-viscous, layers formed which cleared after a few more minutes of standing. The smaller of the two phase volumes at the end point was always much greater than the amount that could be explained on the basis of only pure water coming out.

Procedure for Vapor Pressure of Water Determinations.—A rapid relative method was devised for determining the vapor pressures, and hence the thermodynamic activities, of the solubilized water. The isopiestic principle was utilized in a novel fashion.

The water vapor in the solubilized system was exposed to a salt solution (sodium chloride or calcium chloride) in a weighing bottle suspended from a glass hook attached to the male ground joint of the flask. The solubilized system was stirred magnetically from the outside, as in the solubilization limit studies. The vapor pressure of the water in salt solution was accurately known from standard tables (9). If after several hours the weighing bottle had gained or lost weight, a salt solution of different water activity was substituted. Generally after three such trials it was found that the water activity in the solubilized system could be matched to within about 0.01 unit of activity (activity = unity for pure water) with these "indicator" salt solutions. Thus, within a day or so a series of vapor pressure determinations was completed. Preliminary tests had shown that the usual procedure of equilibrating the solubilized system with an originally unmatched salt solution would have taken weeks.

RESULTS

Solubilization Limit Determinations.—The results of the mole water per mole AOT solubilizable in a single phase state at 30° are given in Fig. 1 as a function of the AOT concentration (w/w). The AOT concentration refers to the AOT-hydrocarbon solution prior to the addition of water. In Fig. 2 the corresponding results at different temperatures are given for octane, dodecane, and hexadecane.

As already mentioned, the precision of the end point determination for a given run was better than 1% but the reproducibility of a point for different AOT starting materials was about $\pm 2\%$. Therefore, in order to minimize the effects of these sample variations upon both the temperature and the AOT concentration dependencies, the same stock AOT sample was used for the results given in Figs. 1 and 2.

The most interesting matter is the extreme sensitivity of the turbidity point to the chain length of the solvent. The behavior is somewhat surprising in view of the negligible chemical differences in the solvents.

Even for the heavy hydrocarbons, hexadecane and

¹ Marketed as Aerosol OT by American Cyanamid Co.

² Variations in the results were as great as 30%.

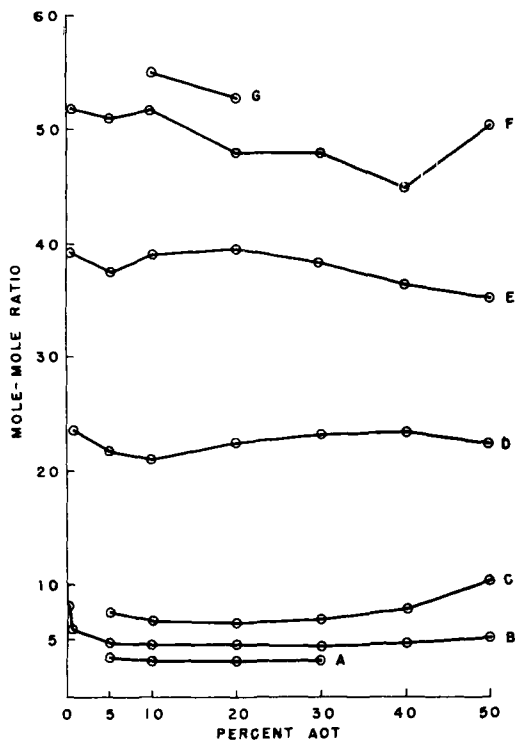


Fig. 1.—The solubilization limit for water in AOT-hydrocarbon systems at 30°. The ordinate is maximum moles of water solubilized per mole AOT. The abscissa is the per cent AOT in hydrocarbon solution prior to addition of water. A, octadecane; B, hexadecane; C, tetradecane; D, dodecane; E, decane; F, octane; and G, heptane.

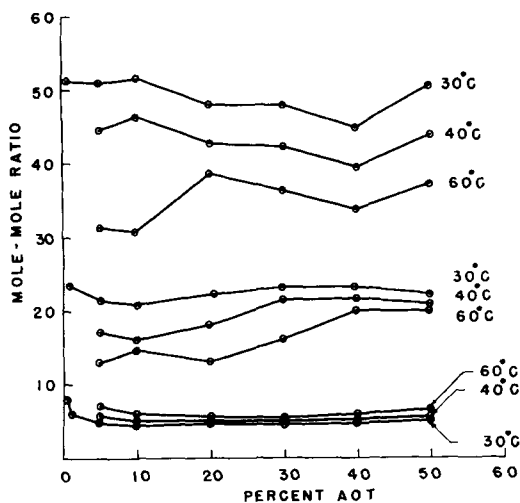


Fig. 2.—The solubilization limit for water in AOT-hydrocarbon systems at different temperatures.

octadecane, four to five moles of water per mole AOT can be sustained in a single phase system. Thus, for the 50% AOT case, it would mean that even here as much as 10% water may be incorporated in a clear preparation.

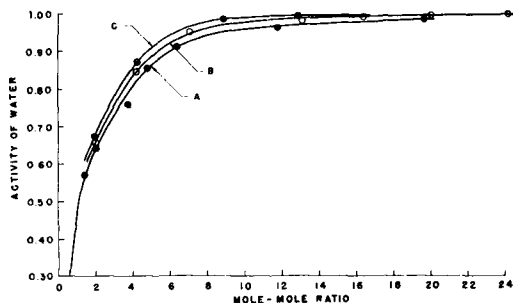


Fig. 3.—The activity of water in AOT-hydrocarbon-water systems as function of mole water per mole AOT solubilized in initially 10% AOT-hydrocarbon solution. A, Hexadecane; B, dodecane; C, octane.

Activity of Water Determinations.—In Fig. 3 the results of the determination of the activity of water (pure water = unit activity) are given for the octane, dodecane, and hexadecane systems at 30° and 10% AOT (in original hydrocarbon solution). The similarity of all three curves suggests that the state of binding of water in the three cases may not be too different, even when compared beyond the hexadecane turbidity point (~5 mole-mole ratio). This at first does appear surprising in view of the great differences in these systems with respect to their solubilization limit behavior.

In the data range reported in Fig. 3 for the octane system the possible condensation of octane in the weighing bottle to give erroneous values was discounted. However, a few activity determinations for the octane system beyond the turbidity point are not reported because there was fogging observed both on the weighing bottle walls and the walls of the flask. The condensing material appeared to be water, and the weighing bottle picked up weight even when pure water was placed in it. These observations suggest that water had just exceeded unit activity at the turbidity point for the octane system.³

Because of the fact that for hexadecane, and possibly for dodecane,⁴ the turbidity point occurred below unit water activity, the solubilization limits as determined here cannot correspond to pure water coming out as the second phase, at least for hexadecane. Therefore, even up to about 20 moles water per mole AOT in the hexadecane case (see Fig. 3), water seems to be in the micellized state even though beyond 5 moles of water the system is no longer a single phase.

DISCUSSION

Mechanism of Solubilization and Solubilization Limit Behavior.—The ultracentrifuge and viscosity studies on the dodecane-AOT-water system by Mathews and Hirschhorn (5) have shown that in this system the water is bound in the interior of spherical monodispersed micelles. Studies by Aebi and Wiebush (7), also on the dodecane system, sug-

³ The water in a water-in-oil emulsion may possess activity slightly greater than bulk water because of the surface-free energy of the droplets.

⁴ As stated, the activity determinations were good to about 1%. For the dodecane system the turbidity occurred at a water activity of 0.99 ± 0.01 , but no fogging of flask or bottle walls was observed at this point.

gest that about one or two moles of water per mole AOT in these micelles are very tightly bound by the polar heads of the AOT while the remainder of the water is "free." This free water is able to dissolve sodium chloride to essentially the same extent as bulk water, except for the common ion effect due to the Na^+ contribution from the AOT itself. In view of the activity data given in Fig. 3, this picture for the state of dispersion of the system should be appropriate for both octane and hexadecane, and therefore for probably all hydrocarbons studied here.

Why then are there such vast differences in the solubilization limits? An unambiguous answer to this question would require more work on this problem. The situation is complex to the extent that a single simple mechanism will not explain all of the facts. In the following paragraphs a tentative, reasonable picture consistent with the main observations is presented.

If it is first postulated that the turbidity point corresponds to the aggregation of intact swollen micelles and that the aggregation tendency is inversely related to the degree of solvation of the exterior of the micelles, the results of these studies can be rationalized. In essence, then, this theory states that the greater the amount of water in the micelle interior the greater the aggregation tendency, and the greater the micelle exterior solvation the lesser the tendency for aggregation. The "intactness" assumption seems reasonable in view of the similarity of the water activity data for hexadecane, dodecane, and octane beyond the hexadecane turbidity point. If the hexadecane turbidity point corresponded to some kind of micelle destruction and consequent rearrangement of hexadecane, water, and AOT molecules, this similarity would be fortuitous.

The tendency for micellar aggregation should be inversely related to how well the outside of the micelles are solvated. The stronger and thicker the solvated layer, the farther apart the polar cores of the micelles will be kept. Therefore, the type of attractive forces (10) responsible for suspension and emulsion aggregation would be minimized.

Solvation would generally be expected to be exothermic. Therefore increase in temperature should generally result in a decrease in solvation. This is consistent with the temperature dependence observed for octane and dodecane (see Fig. 2). If there is no solvation one would expect that an increase in temperature would lessen the tendency for aggregation. This is compatible with the small but positive temperature dependence observed with the hexadecane system.⁵

From a purely statistical point of view, it is reasonable (11) to expect that the lower hydrocarbons might better solvate the micelle than the higher hydrocarbons. The local thermodynamic activity of the externally exposed functional groups of the micelles is greater for higher hydrocarbon systems

because the kinetic units of the solvent are larger for the higher hydrocarbons. Therefore, their tendency to mix with the solvent should be less; the externally exposed groups of the micelle have a greater tendency for intramicellar association in higher hydrocarbons.

The lack of distinct AOT concentration dependence (see Fig. 1) at first thought appears to be contradictory to this theory, but it must be kept in mind that these are concentrated systems and intermicellar interactions are likely to be important. Actually the hexadecane system, for which some low AOT concentration runs were made, does show (see Fig. 1) a rapid increase in the mole-mole ratio with decreasing AOT concentration at low AOT concentrations. This is consistent with the aggregation theory and the mass action concept.

Because for the lower hydrocarbons the activity of micellized water was essentially unity at the turbidity point, there was the likelihood of the presence of emulsion droplets of water in these cases. It is possible that these emulsion droplets were able to nucleate the aggregation in the lower hydrocarbons.⁶ Further discussion of this possibility would be only speculation at this point, however.

Pharmaceutical Significance.—These thermodynamically stable islands of water in oil should provide a means of incorporating ionic and other highly polar drugs into essentially nonpolar vehicles. An example already cited above is the solubilization of sodium chloride in micellized water.

A useful application for these systems should be found in the development of ointments. It would seem that a relatively nondrying ointment base could be designed on these concepts. For highly polar drugs the ointment of this type would, furthermore, possess slow but prolonged release characteristics.

This technique of solubilization might be utilized in the preparation of sustained-action formulations in which the drug can be uniformly and reproducibly dispersed into a wax. Investigations of this possibility are now under way in our laboratories.

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⁵ Temperature dependence for aggregation, *per se*, should be small since the energies involved are only the order of a few kT , where k = Boltzmann's constant and T = absolute temperature.

⁶ Kinetics is not implied here, but that the droplets could provide surfaces for adsorption of micelles, and if some water is released by these micelles upon adsorption, this type of aggregation would perpetuate itself.